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A Nomenclature System for the Isoprostanes

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In 1990, prostaglandin (PG) F_2-like compounds were discovered to be produced in abundance in vivo by a free radical mechanism independent of the cyclooxygenase enzyme. Because these compounds are isomeric to cyclooxygenase-derived $PGF_{2\alpha}$, they were termed F_2-isoprostanes (F_2-IsoP's). Subsequently, it was also demonstrated that PGD_2-like compounds (D_2-IsoP's) and PGE_2-like compounds (E_2-IsoP's) are also produced in vivo as products of this pathway. Four different regioisomers of each of these classes of IsoP's are formed, each of which can be comprised of eight racemic diastereomers. Thus, 64 different F_2-IsoP's, E_2-IsoP's, and D_2-IsoP's can be formed. Interest in these molecules stems not only from the fact that quantification of IsoP's can provide a valuable index of free radical-induced lipid peroxidation in vivo but also from the fact that it has been shown that these compounds are capable of exerting potent biological activity. Because of this potential for exerting biological activity, the chemical syntheses of various IsoP compounds for biological testing has been initiated. As a result, a need for a systematic nomenclature for these compounds has evolved. A facile nomenclature that will allow rational differentiation and designation of each of the isomeric structures comprising the family of IsoP's is presented. © *1997 by Elsevier Science Inc.*

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Introduction

In 1990, we discovered that PGF_2-like compounds are formed in abundance *in vivo* by free radical induced peroxidation of arachidonic acid, independent of the cyclooxygenase enzyme (1). Because these compounds are isomeric to $PGF_{2\alpha}$ derived from the cylooxygenase enzyme, they were termed F_2-isoprostanes (F_2-IsoP's). The formation of F_2-IsoP's proceeds through the formation of PGG_2-like bicyclic endoperoxide intermediates which are then reduced to form F_2-IsoP's. Subsequently, we discovered that PGD_2-like compounds (D_2-IsoP's) and PGE_2-like compounds (E_2-IsoP's) are also formed *in vivo* via rearrangement of the IsoP endoperoxide intermediates (2). Depending on the site of the original arachidonyl radical formed, four regioisomers of the IsoP's are produced, each of which can be comprised of eight racemic diastereomers. Thus, 64 different isomers each of F_2-, E_2-, and D_2-IsoP's can be generated.

Interest in the IsoP's stems not only from the fact that measurement of these compounds appears to represent an important advance in our ability to assess non-enzymatic free radical catalyzed lipid peroxidation *in vivo* as an index of oxidative stress status, but also because these compounds have been shown capable of exerting potent biological activity (reviewed in 3,4). Because of the potential for IsoP's to exert biological activity, the chemical synthesis of IsoP's for biological testing has been undertaken by several groups (5-9). Thus, a need for a systematic nomenclature system for the IsoP's has emerged. Herein, we propose a facile nomenclature system that allows the differentiation of the many isomeric structures that can be formed as products of the IsoP pathway. This system follows standard rules for chemical nomenclature and conforms with prostaglandin convention.

Nomenclature System

First, we propose to abbreviate the term *isoprostanes* as "IsoP". This abbreviation is preferred over "IP" to avoid confusion with inositol phosphates, which have an accepted abbreviation of "IP". The initial reference to the different classes of IsoP's as F_2-, E_2-, and D_2-IsoP's will be retained.

Originally, the IsoP's were divided into four classes (I-IV) to refer to each of the different regioisomers that are formed, exemplified by **1**, **2**, **3**, and **4**, respectively (Figure 1). We now propose to name these four classes by the location of the side chain hydroxyl group, with C-1 being the carboxyl group, consistent with standard prostaglandin nomenclature. Thus, **1** would be a 5-F_2-IsoP, **2** would be an 8-F_2-IsoP, **3** would be a 12-F_2-IsoP, and **4** would be a 15-F_2-IsoP. The analogous nomenclature for

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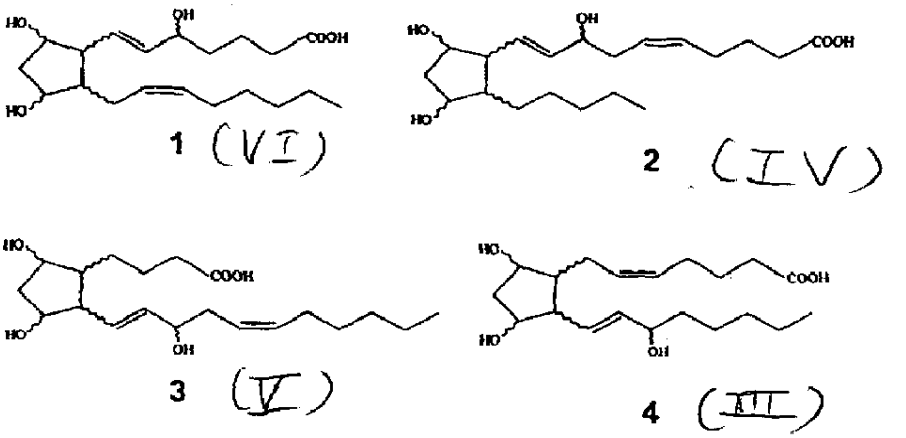

FIGURE 1. Four regioisomers of F_2-IsoP's formed, each of which can be comprised of eight racemic diastereomers.

the other IsoP classes would be 5-E_2-IsoP, 5-D_2-IsoP, *etc.* We propose that the default absolute configuration for the side chain hydroxyl is (S).

Owing to the fact that F_2-IsoP's are formed from the reduction of IsoP endoperoxide intermediates, the ring hydroxyls must be oriented *cis* inrelation to the cyclopentane ring. We propose that the default absolute configuration for the ring hydroxyls is down (α). If the ring hydroxyls are oriented up (β), the compound would be designated as the enantiomer (*ent*). The default absolute configuration of the side chain hydroxyl in the enantiomeric (*ent*) series is (R).

Although the side chains of IsoP's are predominantly oriented *cis* in relation to the cyclopentane ring (1), compounds with the side chains oriented *trans* to the ring can also be formed. If the side chains are oriented *trans* in relation to the ring, the lower number carbon will be designated *epi*, consistent with standard chemical nomenclature rules.

Compounds are then further delineated in relation to whether the side chains are oriented *trans* or *cis* in relation to the cyclopentane ring hydroxyls (Figure 2). Thus, **5** would be 5-F_{2t}-IsoP, pronounced "5-F-2-trans-isoprostane", **6** would be 5-F_{2c}-IsoP, **7** would be 5-epi-5-F_{2t}-IsoP, **8** would be *ent*-5-F_{2c}-IsoP, **9** would be 8-epi-5-F_{2t}-IsoP, and **10** would be *ent*-8-epi-F_{2t}-IsoP. In accordance with this system when designating E_2- and D_2-IsoP's, **11** would be *ent*-12-E_{2c}-IsoP and **12** would be 15-epi-15-D_{2t}-IsoP. One of the F_2-IsoP's that has received considerable attention because it has been shown exert potent biological activity which may result from an interaction with a novel "IsoP receptor", and methods for its measurement have been developed, is 8-epi-$PGF_{2\alpha}$ (or 8-iso-$PGF_{2\alpha}$) **13** (1,3,4,10,11). Reference to this compound as a prostaglandin misses the distinction between cyclooxygenase derived prostanoids and IsoP's. Thus,

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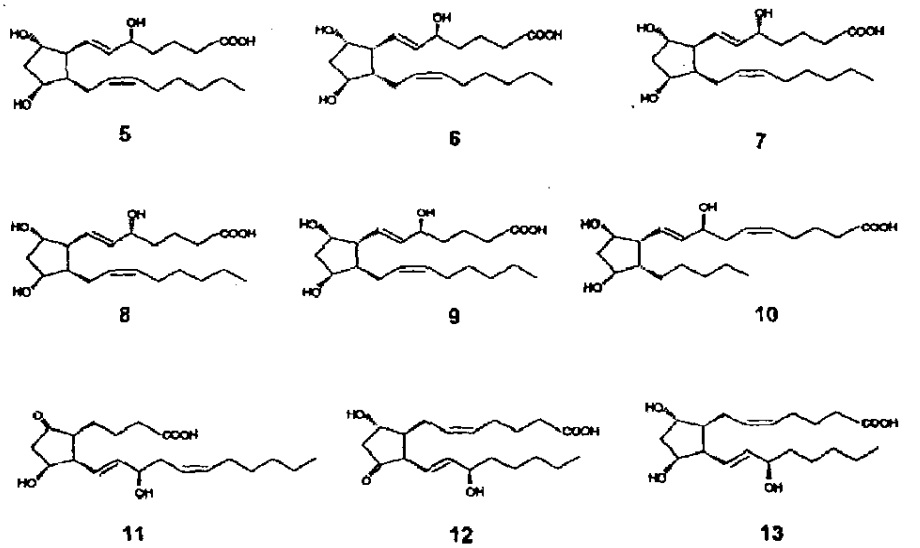

FIGURE 2. Selected different F_2-, E_2-, and D_2-IsoP isomers formed to exemplify the application of the proposed nomenclature system (see text for explanation).

in accordance with the proposed nomenclature, 13 should henceforth be designated as 15-F_{2t}-IsoP.

It is difficult, if not impossible, to design a nomenclature to differentiate the 192 different IsoP's comprised in the F_2-, E_2-, and D_2-IsoP families without some inherent complexities. However, we have attempted to minimize such complexities with the system proposed herein. We feel that this system is flexible, easy to recall, and not unduly cumbersome.

Acknowledgments

This proposed isoprostane nomenclature system has been filed with the Eicosanoid Nomenclature Committee, sanctioned by JCBN of IUPAC. Supported in part by grants GM42056, GM15431, and DK48831 from the National Institutes of Health.

References

1. Morrow, J.D., Hill, K.E., Burk, R.F., Nammour, T.M., Badr, K.F., and Roberts, L.J., II. A series of prostaglandin F_2-like compounds are produced *in vivo* in humans by a non-cyclooxygenase free radical catalyzed mechanism. Proc. Natl. Acad. Sci. USA 87:9383, 1990.
2. Morow, J.D., Minton, T.A., Mukundan, C.R., Campbell, M.D., Zackert, W.E., Daniel, V.C., Badr, K.F., Blair, I.A., and Roberts, L.J., II. Free radical induced

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generation of isoprostanes *in vivo*. Evidence for the formation of D-ring and E-ring isoprostanes. J. Biol. Chem. 269:4317, 1994.

3. Morrow, J.D., and Roberts, L.J., II. The isoprostanes: current knowledge and directions for future research. Biochem. Pharmacol. 51:1, 1996.
4. Roberts, L.J., II, and Morrow, J.D. Generation and actions of isoprostanes. Biochim. Biophys. Acta, in press.
5. Larock, R.C., and Lee, N.H. Organopalladium approaches to prostaglandins. 11. synthesis of $PGF_{2\alpha}$ and 12-epi-$PGF_{2\alpha}$ by the controlled, one step, palladium-promoted intermolecular coupling of three different alkenes. J. Am. Chem. Soc. 113:7815, 1991.
6. Vionnet, J-P., and Renaud, P. Facile preparation of 12-epiprostaglandins from 7-oxabicyclo [2.2.1] hept-5-en-2-one via an all-cis-formyllactone related to Corey lactone. Helv. Chim. Acta 77:1781, 1994
7. Hwang, S.W., Adiyaman, M., Khanapure, S.P., Schio, L., and Rokach, J. Total synthesis of 8-epi-$PGF_{2\alpha}$. A novel strategy for the synthesis of isoprostanes. J. Am. Chem.Soc. 116:10829, 1994.
8. Adiyaman, M., Lawson, J.A., Hwang, S-W., Khanapure, S.P., Fitzgerald, G.A., and Rokach, J. Total synthesis of a novel isoprostane $IPF_{2\alpha}$ and its identification in biological fluids. Tetrahedron Lett. 37:4849, 1996.
9. Taber, D.F., and Hoerner, R.S. Enantioselective Rh-mediated synthesis of (-)-PGE_2 methyl ester. J. Org. Chem. 57:441, 1992.
10. Wang, Z., Ciabattoni, G., Creminon, C., Lawson, J., Fitzgerald, G.A., Patrono, C., and Maclouf, J. Immunologic characterization of urinary 8-epi-prostaglandin $F_{2\alpha}$ excretion in man. J. Pharmacol. Exp. Therap. 275:94, 1995.
11. Bachi, A, Zuccato, E., Baraldi, M, Fanelli, R., and Chiabrando, C. Measurement of urinary 8-epi-prostaglandin $F_{2\alpha}$, a novel index of lipid peroxidation in vivo, by immunoaffinity extraction/gas chromatography-mass spectrometry. Free Rad. Biol. Med. 20:619, 1996.

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